REMARKS

Claims 1-6, 8, 16, 18, 22-27, 30 and 31 were pending and under examination in this case. Claims 28 and 29 are withdrawn. With this reply, claim 22 has been cancelled and claim 32 has been added. Thus, claims 1-6, 8, 16, 18, 23-27, and 30-32 are now pending and under examination. Claims 1-6, 8, 16, 18, 22, 24, and 25 stand rejected under 35 U.S.C. § 102, and all claims stand rejected under 35 U.S.C. § 103. These rejections are addressed below.

Rejections under 35 U.S.C. § 102

Claims 1-6, 8, 16, 18, 22, 24, and 25 stand rejected as being anticipated by Deckers et al. or Bobier-Rival et al. This rejection is respectfully traversed.

As a basis for this rejection, the Office Action at page 3 states:

> It is noted that green tea contains the claimed mixture of polyphenols inherently since the polyphenols recited in claim 1 all come from green tea thus they all must in an extract of green tea since that is where they come from, thus the claims are anticipated by the references.
>
> … as noted by applicants in their specification at col. 4, lines 15-20, the term "about" means according to the invention a general error range of +/- 20%, especially +/- 10%, in particular +/- 5%. This error range could then be very small amounts such as 0.05 to amounts such as 40 % according to the information in the specification. Applicants argue that this "error range" is 20 % of the lowest or the highest but that is not what the specification says. The specification very clearly gives amounts 20% above and below, 5-20 %, thus clearly reading on the references.

Applicants respectfully disagree. At paragraph 13 of the specification (page 2), Applicants have defined an error range, expressed as a percentage, to define the term 'about' in reference to a recited numerical value. Such an approach is commonly used to define a range based upon some fraction of the numerical value recited. For example a ± 20% error in the value 5 is 5 ± 1 ($5 \times (20/100) = 1$). In the instance of the present claims, the recited values are weight percentages. Because both the numerical value and the error range are expressed as percentages, the Office has decided that the errror range should be applied additively, not fractionally. However, to do so yields mathematically nonsensical results in which the error range encompasses negative weight percents. For example, applied additively an error of ± 20% on a weight percentage of 5% produces a range of minus 15% to plus 25% weight percent. This approach is clearly contrary to the teachings of the specification in which the pharmaceutically effective amount must clearly include some amount of polyphenol. Rather, and as is consistent with standard terminology in this field, the error ranges are calculated fractionally.

With this reply, claim 1, and dependent claims 2-6, 8, 16, 18, and 23-32, have been amended to clarify that the claimed method for treating actinic keratosis includes administering to the subject a composition containing a specific percentage by weight of polyphenols (i.e., claim 1 recites a range of 5 ± 1% (w/w) to 20 ± 4% (w/w)). To avoid confusion, Applicants have performed the fractional calculation of the error on the lower and upper limits of the recited range, ± 20% of 5% and 20%, respectively. Applicants note that the term 'about' was earlier removed from claim 1.

Nowhere is a composition for treatment of actinic keratosis including this specific weight percentage of polyphenols disclosed in the art.

Deckers describes the use of emulsions in products for topical application to the skin (see Abstract) where one of numerous possible applications is the treatment of actinic keratosis (col. 25, lines 17-18). One possible ingredient of the emulsion is an anti-oxidant (col. 19, line 32) and among the anti-oxidants which can be used is listed green tea extract (col. 23, lines 1-12). With respect to anti-oxidants, Deckers, at col. 13, lines 21-28, recites:

> Generally, the emulsion formulations will be treated such that contamination by bacteria, fungi, mycoplasmas, viruses and the like or undesired chemical reactions, such as oxidative reactions are prevented. In preferred embodiments this is accomplished by the addition of preservatives, for example sodium metabisulfite; Glydant Plus; Phenonip; methylparaben; propylparaben; Germall 115; Germaben II; phytic acid; and mixtures thereof.

And at col. 13, lines 36-41, recites:

> Oxidative reactions may be prevented by the addition of anti-oxidants such as for example butylated hydroxytoluene (BHT); butylated hydroxyaniscol (BHA); ascorbic acid (vitamin C); tocopherol; phytic acid; citric acid; pro-vitamin A; and mixtures thereof.

Nowhere in Deckers are there any specific examples of formulations that include green tea extract and nowhere is there any teaching of what amounts of green tea extract would be used. Furthermore, nowhere in Deckers is there a teaching or suggestion to use green tea extract for any purpose other than for use as an anti-oxidant. Thus, Deckers teaches nothing more than an amount of green tea extract consistent with its use as an anti-oxidant.

The amount of green tea extract suitable for use as an anti-oxidant is found in Hara (U.S. Patent No. 4,673,530; already of record), which describes a process for the production of anti-oxidants from green tea leaves. Hara teaches that, in their system, the effective anti-oxidant potency of green tea extract exceeds that observed for dl-α-tocopherol (vitamin E) and butylated hydroxy anisol (BHA) (see Hara from col. 2, line 65, to col. 3, line 3; as well as Figures 1-3), indicating to one of skill in the art that a relatively small amount of green tea extract would have an anti-oxidant effect.

The Deckers formulations include anti-oxidants only in very small amounts; for example, Examples 7-10 of Deckers include 0.05% (w/w) vitamin E acetate and Examples 6, 11, 13, and 15 include 0.1% butylated hydroxy anisol (BHA) and 0.1% butylated hydroxy toluene (BHT). Notably, the anti-oxidants used by Deckers were shown by Hara to be less effective at preventing oxidation than green tea extract. Accordingly, a yet smaller amount of green tea extract would be required to achieve the goal of producing an anti-oxidant effect.

At most, Deckers' disclosure is sufficient to place one of skill in the art with a composition for treating actinic keratosis that contains around 0.1% (w/w) green tea extract. Assuming, for the sake of argument, that all other claim limitations are met, Deckers would still not anticipate any of the pending claims because the low amounts of green tea extract for the purposes taught by Deckers are at least **40 times lower** than the lowest value (5 ± 1% (w/w) polyphenols) encompassed by the range recited in claim 1. The rejection in view of Deckers should be withdrawn.

Bobier-Rival describes the use of a cosmetic or dermatological composition containing a skin enhancing agent (see Abstract). One of the possible classes of skin enhancing agents is retinoids, which are known to be used in dermatology for treating actinic keratoses (see Abstract and col. 1, lines 33-34). Most importantly, the only mention of tea extract in Bobier-Rival is in the formulation of Example 1 spanning columns 4 and 5. Example 1 describes the preparation of an oil phase containing 19.7 grams of components and an aqueous phase containing 66.43 grams of components. These two phases were then mixed to form a carrier emulsion to which were added the active ingredients: salicylic acid in ethanol (3.5 grams), Lipomicron® (6 grams), Vitamin A palmitate (0.1 grams), and Luzenac talc (3 grams). The total mass of materials used in the formulation was 98.73 grams. A 2% green tea extract was contained within 10 grams of lactic acid solution, a component of the aqueous phase. Accordingly, the total mass of green tea extract in the formulation is 0.2 grams (10 × 0.02). The w/w percentage of green tea extract in the formulation is 0.20% ((0.2 ÷ 98.73) × 100).

Again, assuming, for the sake of argument, that all other claim limitations are met (which Applicants do not concede), Bobier-Rival would still not anticipate any of the pending claims because the 0.20% (w/w) green tea extract taught by Bobier-Rival is **20 times lower** than the lowest value (5 ± 1% (w/w) polyphenols) encompassed by the range recited in claim 1.

Thus, neither Deckers nor Bobier-Rival teach or suggest administering to a subject a composition containing from 5 ± 1% (w/w) to 20 ± 4% (w/w) mixed polyphenols for the treatment of actinic keratosis, as required by claim 1 and dependent claims 2-6, 8, 16, 18, and 23-31.

Because Deckers and Bobier-Rival fail to teach or suggest this claim limitation, these references do not anticipate the pending claims. Applicants request that the rejections for lack of novelty be withdrawn.

Rejections under 35 U.S.C. § 103

Claims 1-6, 8, 16, 18, and 22-27 stand rejected, under 35 U.S.C. § 103(a), as being unpatentable over Hsu in combination with Miller et al. Claims 1-6, 8, 16, 18, and 22-27 stand further rejected, under 35 U.S.C. § 103(a), as being unpatentable over Deckers or Bobier-Rival in combination with Miller et al. These rejections are respectfully traversed.

As a basis for the rejection over Hsu in view of Miller, the Office Action at page 5 states:

> Hsu teaches a mixture of green tea polyphenols which are used topically in ointment form to treat actinic keratosis, see claims, paragraphs 65 and 66. Hsu also teaches that an additive such as a wax can also be included with the composition, see paragraph 85. The concentrations and types of green tea polyphenols are inherent to the green tea extract. No special method of extraction of the polyphenols from the green tea is disclosed in the instant specification thus the green tea disclosed in Hsu must contain the same polyphenols and in the same amounts as claimed. The compositions are also administered to a human, see paragraph 27.

and at pages 6 and 7 states:

> Applicant argues that Hsu does not constitute prior art but it does since the provisional application was filed 12/10/2002 and the disclosure at page 84 clearly teaches that actinic keratosis may be useful topically to treat actinic keratosis. Applicant argued that it was not anticipatory which is agreed with thus the 35 USC 102 rejection is withdrawn but under 35 USC 103 it is deemed obvious to use the green tea extract to treat actinic keratosis since it is clear that Hsu clearly intended to treat actinic keratosis with the green tea since it may work. The motivation is that knowing the disclosure of Hsu one of ordinary skill in the art would be clearly motivated to treat actinic keratosis with the green tea since it is clear that one may treat actinic keratosis with the green tea as noted by Hsu at page 84.

and at page 7 states:

> Applicant argues that Hsu doubts whether green tea components could be used to treat actinic keratosis. It is very clear from Hsu at paragraphs 14 and 19, that actinic keratosis is one of the skin disorders that clearly can be treated with polyphenols and that green tea which contains the polyphenols can be used in such a method.

Applicants respectfully disagree. For the obviousness rejections, the Office has again dismissed the recited w/w percentages of mixed polyphenols recited in the claims. This issue is addressed in the remarks above.

As indicated on its face, the Hsu reference is a publication of a U.S. application filed December 10, 2003, which claims the benefit of a provisional application filed December 10, 2002. Applicants' effective filing date intervenes, falling on October 9, 2003. Thus, the only subject matter in Hsu that constitutes prior art to the claimed invention under 35 U.S.C. § 102(e) is material disclosed in the Hsu provisional application.

While the Office appears to acknowledge this fact, this latest rejection for obviousness over Hsu by the Office nonetheless is based, in part, on subject matter present only in the Hsu utility application. For example, the subject matter of paragraphs 14, 19, 27, 65, 66, and 85 are relied upon by the Office in making this rejection. However, all of these paragraphs were added after Applicants' filing date and, therefore, are not prior art to the pending claims.

Relying solely upon the subject matter of the provisional filing, Hsu et al. discloses on page 84, 3rd paragraph that "green tea components may be useful topically for...treatment of....actinic keratosis." However, Hsu et al. does not give any indication what components of green tea are necessary or sufficient to treat actinic keratosis. Furthermore, Hsu et al. expresses doubts about whether green tea components could be used to treat actinic keratosis. Hsu explicitly states that green tea components may be useful for this type of treatment, and in no way discloses what those green tea components would be. It is thus contradictory to the explicit teaching of Hsu – who states that it is unclear whether actinic keratoses can be treated with green tea components or what those components would be – to take the position that Hsu provides a reasonable expectation of successfully arriving at Applicants' invention.

In addition, Hsu does not teach or suggest administering to a subject a composition containing from 5 ± 1% (w/w) to 20 ± 4% (w/w) mixed polyphenols for the treatment of actinic keratosis, as required by claim 1 and dependent claims 2-6, 8, 16, 18, and 23-31.

The secondary reference fails to cure these deficiencies in the Hsu teaching. Miller teaches only that curettage may be used to treat actinic keratoses, never disclosing or suggesting the use of any polyphenol mixtures for actinic keratosis therapy. This first basis for § 103 rejection of the claims should be withdrawn.

Claims 1-6, 8, 16, 18, and 22-27 stand further rejected, under 35 U.S.C. § 103(a), as being unpatentable over Deckers or Bobier-Rival in combination with Miller et al.

As noted above, neither Deckers nor Bobier-Rival teach or suggest administering to a subject a composition containing from 5 ± 1% (w/w) to 20 ± 4% (w/w) mixed polyphenols for the treatment of actinic keratosis. Furthermore, both Deckers and Bobier-Rival fail to provide any teaching or suggestion that green tea extracts are, by themselves, useful for the treatment of actinic keratosis.

The presence of green tea extract as a minor component in a formulation for the treatment of actinic keratosis, but without any recognition of its specific therapeutic benefit, when present in effective amounts, is insufficient to render the pending claims obvious in view of these references.

Further, as noted above, Miller teaches only that curettage may be used to treat actinic keratoses, never disclosing or suggesting the use of any polyphenol mixtures for actinic keratosis therapy. Accordingly, Miller fails to cure the deficiencies in Deckers and Bobier-Rival.

In addition, on the issue of obviousness, Applicants further draw the Examiner's attention to that fact that Applicants have demonstrated unexpectedly good results for the claimed invention. Indeed, it was entirely unanticipated that actinic keratoses would disappear completely following Applicants' claimed treatment. As demonstrated by the results presented in Examples 1 and 2 of the present application, in patients suffering from actinic keratoses for at least 10 years, treatment with Polyphenon E, an exemplary polyphenol mixture of the claims, resulted in resolution of *all keratoses* exhibited by the patients within *only 12-16 weeks*. This complete and rapid therapeutic effect was striking and would be considered by those of skill in this area to constitute an unexpectedly good result. For this reason as well, the present invention cannot be considered obvious, and the § 103 rejection should be withdrawn.

Support for Amendments to the Claims

Support for new claim 32 is found in the specification at paragraph 51 and in Examples 1 and 2, describing the effect of Polyphenon E on actinic keratoses.

Claim 1 has been amended to clarify that actinic keratosis is treated by administering a composition including mixed phenols and a carrier. Support for this amendment is found in the specification from paragraph 53 to paragraph 61.

Claims 16, 18, 23, 24, and 25 have been amended to provide proper antecedent basis for limitations relating to mixed phenols and limitations relating to the carrier.

Support for the a composition comprising from 5 ± 1% (w/w) to 20 ± 4% (w/w) mixture of polyphenols, as recited in claim 1; from 10 ± 1% (w/w) to 20 ± 2% (w/w) as recited in claim 30; and 15 ± 3% (w/w) mixture of polyphenols as recited in claim 31 is found in the specification at paragraphs 12 and 13. As noted above, the errors recited in paragraph 13 have been fractionally applied to the effective amounts listed in paragraph 12 and the term 'about' has been removed from claims 1, 30, and 31.

No new matter has been added with these amendments.

CONCLUSION

Applicants submit that this case is now in condition for allowance, and such action is respectfully requested.

Enclosed is a Petition to extend the period for replying to the Office action for 3 months, to and including July 30, 2008, and a check in payment of the required extension fee.

To expedite prosecution Applicants request a telephonic interview with the Examiner to discuss any remaining rejections. The Examiner is invited to call the undersigned at 617-428-0200.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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Karen L. Elbing, Ph.D.
Reg. No. 35,238

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045